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10/530,658	04/07/2005	Maria Foti	100506-00025	9098

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EXAMINER
LEE, JAE W

ART UNIT	PAPER NUMBER
1656	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/530,658	FOTI ET AL.	
	Examiner	Art Unit	
	JAE W. LEE	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 May 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4 and 6-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4 and 6-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 May 2008* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Application status

In response to the previous Office action, a non-Final rejection (mailed on 02/22/2008), Applicants filed a response and amendment received on 05/22/2008. Said amendment canceled Claim 5, and amended Claims 1, 6, 8, 13-17 and 23. Thus, Claims 1-4 and 6-24 are at issue and present for examination.

Applicants' arguments filed on 05/22/2008, have been fully considered, and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

The text of those sections of Title 35 U.S. Code not included in the instant action can be found in a prior Office action.

Drawings

The previous objection to the drawings is maintained because the Figure 3 as provided is very difficult to read. Specifically, the background of the graphs in Figure 3 are very dark, thus it's not possible to distinguish the lines or data from the background. It is also noted that all Figures 1-5 are difficult to read because of the dark background. The Examiner suggests getting rid of the dark background so that the data provided by the Applicants are clear.

Appropriate correction is required.

Claim Objections

The previous objection of Claims 8 and 18 for reciting "SEQ. N." is withdrawn by virtue of Applicants' amendment.

Claims 2-4, 19, 21 and 23 are objected to because of the following informalities:

Claims 2-4 are objected to because they can be substantially improved with respect to form. The Examiner suggests reciting ---wherein said corresponding region of Clytin photoprotein is identical to said region of Obelin protein that is to be replaced with the exception of at least 1 [5 or 10 for claims 3 and 4, respectively] amino acid residue--- to the extent that it is Applicants' intent.

Claims 14-17 are objected to because the claimed method can be substantially improved with respect to form. The reason is that there is no positive steps indicating how to detect calcium ions with the recited products. The Examiner suggests adding additional active steps for indicating how calcium ions are detected with the recited products.

Claim 19 and 21 recite the phrases, "The cellular host of claim 18" and "a cellular host according to claim 18," respectively which can be improved with respect to form. The Examiner suggests replacing the note phrases with ---The host of claim 18--- and ---the host according to claim 18---, respectively.

Claim 21 is objected to because the claimed method can be improved with respect to clarity. It appears that the steps of (A) measuring luminescent signal after exposing the host cell of claim 18 to a biologically active molecule that may increase or

decrease the intracellular calcium concentration, and (B) comparing the result obtained in step (A) with that of a control, are missing prior to carrying out "detecting any variation of intracellular calcium concentration" according to the Example 3 of the specification on pages 10-12.

Claim 23 is objected to because it can be improved with respect to consistency. The Examiner suggests replacing "a conjugation product according to claim 11" with --- the conjugation product according to claim 11---.

Claim 23 is objected to because the claimed method can be improved with respect to clarity. It appears that the steps, describing how one can determine the amount of the conjugation product of claim 11 for therapeutic use, are missing.

Appropriate correction is required.

Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The previous rejection of Claims 1-24 under 35 U.S.C. § 112, second paragraph, is withdrawn because Applicants have deleted the phrase, "a region of Obelin protein comprised between the first and the second calcium binding sites."

Claims 1-4 and 6-24 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recite the phrase, "a region of Obelin protein with a corresponding region of Clytin photoprotein, wherein said region is located between residue 42 and 122 of the Obelin protein sequence (SEQ ID NO: 2)," which is unclear and indefinite for the following reasons:

[1] It is unclear respect to what is encompassed by "a corresponding region of Clytin photoprotein." It is also unclear how the regions of Obelin and Clytin photoproteins correspond to each other. Do they correspond to each other with respect to structure, function or both, and if they correspond with respect to structure, function or both, then under what criteria?

[2] It is unclear with respect to what "a region ... wherein said region is located between residue 42 and 122 of Obelin protein sequence" is referring to. If Applicants are referring to a genus of Obelin proteins where a region can be replaced, how can the region to be replaced in these proteins be located between two residues of a single protein? The Examiner suggests either amending the phrase "obtained by replacing a region of Obelin protein" to ---obtained by replacing a region of the Obelin protein of SEQ ID NO:2---, or deleting the phrase "wherein said region is located between...." and define the region to be replaced so that it would apply to the entire genus of Obelin proteins, for example, ---wherein the region to be replaced in the Obelin protein corresponds to residues 42-122 of the protein of SEQ ID NO:2---. This is assuming that

Applicants have support in the specification for such an amendment. In the interest of advancing prosecution, the noted phrase is interpreted as "A chimeric photoprotein obtained by replacing any region of Obelin protein with any region of Clytin photoprotein."

Claims 2-4 recite the limitation "the selected photoprotein" in Claims 1-3. There is insufficient antecedent basis for this limitation in the claim.

Claims 6, 7 and 9 are unclear and indefinite because they all refer to a region of Obelin, a fragment of Clytin sequence or specific substitution positions in Obelin sequence without a reference to a specific sequence, i.e., SEQ ID NO, which are undefined in claim 1 (see above 112 2nd paragraph rejection). As such, it is not clear what these numbers, supposedly indicating regions/fragments/positions, are referring to.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4 and 6-24 are rejected under 35 U.S.C. § 112, first paragraph, written description, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to

reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The rejection was stated in the previous office action as it applied to previous claims 1-24. In response to this rejection, Applicants have cancelled claim 5, and amended claims 1, 6, 8, 13-17 and 23, and traverse the rejection as it applies to the newly amended claims.

Applicants argue that based on their amendment to claim 1, which limits the photoprotein to the Clytin photoprotein, Applicants assert that they meet the written description requirement under 112 1st paragraph.

Applicants' arguments have been fully considered but are not deemed persuasive for the following reasons. The instant claims are directed to genera of (1) chimeric photoproteins obtained by replacing any region of a genus of Obelin proteins (see 112 2nd paragraph rejection above) with any corresponding region of Clytin photoprotein (see 112 2nd paragraph above); (2) any fusion protein containing the photoprotein of claim 1; (3) any conjugation product between a photoprotein according to claim 1 and a molecule for analytical, diagnostic or therapeutic use; (4) any isolated nucleic acid molecule encoding a chimeric photoprotein according to claim 1; (5) a method for detecting calcium ions, comprising using the chimeric photoprotein according to claim 1, in combination with a luciferin substrate; (6) a host cell bearing any nucleic acid molecule according to claim 12; (7) a method for producing a photoprotein, which comprises growing the host cell of claim 18 in conditions suitable for photoprotein expression, and recovering the expressed protein; (8) a method for the screening of

biologically active molecules, which comprises exposing a cellular host according to claim 18 to a definite amount of said molecules and detecting any variation of intracellular calcium concentration; (9) a method of determining the amount of a molecule for analytical, diagnostic or therapeutic use, comprising using the conjugation product according to claim 11 in a competitive solid-phase immunoassay for determining the amount of said molecule in biological samples; and (10) a bioluminescence resonance energy transfer (BRET) system, comprising a fluorescent protein and any photoprotein of claim 8. As such, contrary to Applicants' allegation, the genus of claimed chimeric photoproteins are not limited with respect to its structure and function. Rather, as amended, the genus of chimeric photoproteins encompassed by claim 1 includes a chimeric photoprotein obtained by replacing any region with any fragment of Clytin photoprotein, wherein said genus does not have to have any desired biological function, i.e., bioluminescence and maintaining its ability to interact with calcium ions (see 112 2nd paragraph rejection above). Further, the specification does not provide adequate written description for the genus of claimed chimeric photoproteins, especially respect to how such broad genus of structures correlates with the desired biological function, i.e., bioluminescence and maintaining its ability to interact with calcium ions, so that one of skill in the art would recognize that Applicants' were in possession of the genus at the time of filing. It is noted by the Examiner that the specification discloses only a single representative species of a chimeric photoprotein comprising the amino acid sequence as set forth in SEQ ID NO: 3, encoded by the

nucleic acid sequence as set forth in SEQ ID NO: 4. For the reasons provided herein and in the previous office action, the rejection under this statute is maintained.

Claims 1-4 and 6-24 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement, because the specification, while being enabling for a chimeric photoprotein comprising the amino acid sequence as set forth in SEQ ID NO: 3, encoded by the nucleic acid sequence as set forth in SEQ ID NO: 4, does not reasonably provide enablement for (1) any chimeric photoproteins obtained by replacing any region of Obelin proteins (see 112 2nd paragraph rejection above) with any corresponding region of Clytin photoprotein (see 112 2nd paragraph above); (2) any fusion protein containing the photoprotein of claim 1; (3) any conjugation product between a photoprotein according to claim 1 and a molecule for analytical, diagnostic or therapeutic use; (4) any isolated nucleic acid molecule encoding a chimeric photoprotein according to claim 1; (5) a method for detecting calcium ions, comprising using the chimeric photoprotein according to claim 1, in combination with a luciferin substrate; (6) a host cell bearing any nucleic acid molecule according to claim 12; (7) a method for producing a photoprotein, which comprises growing the host cell of claim 18 in conditions suitable for photoprotein expression, and recovering the expressed protein; (8) a method for the screening of biologically active molecules, which comprises exposing a cellular host according to claim 18 to a definite amount of said molecules and detecting any variation of intracellular calcium concentration; (9) a method of determining the amount of a molecule for analytical, diagnostic or therapeutic use,

comprising using the conjugation product according to claim 11 in a competitive solid-phase immunoassay for determining the amount of said molecule in biological samples; and (10) a bioluminescence resonance energy transfer (BRET) system, comprising a fluorescent protein and any photoprotein of claim 8, as encompassed by the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The rejection was stated in the previous office action as it applied to previous claims 1-24. In response to this rejection, Applicants have cancelled claim 5, and amended claims 1, 6, 8, 13-17 and 23, and traverse the rejection as it applies to the newly amended claims.

Applicants argue that the specification provides adequate guidance for one skilled in the art to carry out the present invention. In addition, Applicants submit that the presently amended claims now reflect a chimeric photoprotein obtained by replacing a region located between residue 42 and 122 of the Obelin protein sequence with a corresponding region of the Clytin photoprotein. Applicants allege that those skilled in the art would be able to generate chimeric photoproteins with enhanced bioluminescence without undue experimentation using the guidance provided in specification.

Applicants' arguments have been fully considered but are not deemed persuasive for the following reasons. The instant claims are directed to genera of (1) chimeric photoproteins obtained by replacing any region of Obelin proteins (see 112 2nd

paragraph rejection above) with any corresponding region of Clytin photoprotein (see 112 2nd paragraph above); (2) any fusion protein containing the photoprotein of claim 1; (3) any conjugation product between a photoprotein according to claim 1 and a molecule for analytical, diagnostic or therapeutic use; (4) any isolated nucleic acid molecule encoding a chimeric photoprotein according to claim 1; (5) a method for detecting calcium ions, comprising using the chimeric photoprotein according to claim 1, in combination with a luciferin substrate; (6) a host cell bearing any nucleic acid molecule according to claim 12; (7) a method for producing a photoprotein, which comprises growing the host cell of claim 18 in conditions suitable for photoprotein expression, and recovering the expressed protein; (8) a method for the screening of biologically active molecules, which comprises exposing a cellular host according to claim 18 to a definite amount of said molecules and detecting any variation of intracellular calcium concentration; (9) a method of determining the amount of a molecule for analytical, diagnostic or therapeutic use, comprising using the conjugation product according to claim 11 in a competitive solid-phase immunoassay for determining the amount of said molecule in biological samples; and (10) a bioluminescence resonance energy transfer (BRET) system, comprising a fluorescent protein and any photoprotein of claim 8. As such, contrary to Applicants' allegation, the claimed chimeric photoproteins are not limited with respect to its structure and function. Rather, as amended, the photoproteins as recited in claim 1 include any chimeric photoprotein obtained by replacing any region with any fragment of Clytin photoprotein, which does not have to have any desired biological function, i.e., bioluminescence and

maintaining its ability to interact with calcium ions (see 112 2nd paragraph rejection above). Further, the disclosure of the specification is limited to a chimeric photoprotein comprising the amino acid sequence as set forth in SEQ ID NO: 3, encoded by the nucleic acid sequence as set forth in SEQ ID NO: 4, and does not provide adequate guidance for making and using any chimeric photoproteins as explained above.
In light of the notion that proteins having very different structures can have the same function (Kisselev et al, 2002), while proteins having very similar structure can have different activities (Witkowski et al, 1999; Wishart et al, 1995), it would require undue experimentation for one of skill in the art to make any chimeric photoprotein by replacing any region of Obelin with any fragment of Clytin in order to obtain those that retain the desired biological function, i.e., bioluminescence and maintaining its ability to interact with calcium ions, so that they can be used in methods of detecting intracellular calcium concentration. For the reasons provided herein and in the previous office action, the rejection under this statute is maintained.

Conclusion

Claims 1-4 and 6-24 are rejected for the reasons as stated above. Applicants must respond to the objections/rejections in this Office action to be fully responsive in prosecution.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jae W. Lee whose telephone number is 571-272-9949. The examiner can normally be reached on 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr Bragdon can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a

USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/JAE W LEE/

Examiner, Art Unit 1656

/Delia M. Ramirez/

Delia M. Ramirez, Ph.D.
Primary Examiner, Art Unit 1652